UNITED STATES PATENT AND TRADEMARK OFFICE

UNITED STATES DEPARTMENT OF COMMERCE
United States Patent and Trademark Office
Address: COMMISSIONER FOR PATENTS
P.O. Box 1450
Alexandria, Virginia 22313-1450
www.uspto.gov

APPLICATION NO.	FILING DATE	FIRST NAMED INVENTOR	ATTORNEY DOCKET NO.	CONFIRMATION NO.
10/051,497	01/18/2002	Rong-Hwa Lin	A0871.70000US01	1774

23628 7590 09/05/2008
WOLF GREENFIELD & SACKS, P.C.
600 ATLANTIC AVENUE
BOSTON, MA 02210-2206

EXAMINER	
GAMBEL, PHILLIP	
ART UNIT	PAPER NUMBER
1644	
MAIL DATE	DELIVERY MODE
09/05/2008	PAPER

Please find below and/or attached an Office communication concerning this application or proceeding.

The time period for reply, if any, is set in the attached communication.

Office Action Summary	Application No.	Applicant(s)	
	10/051,497	LIN ET AL.	
	Examiner	Art Unit	
	Phillip Gambel	1644	

-- The MAILING DATE of this communication appears on the cover sheet with the correspondence address --

Period for Reply

A SHORTENED STATUTORY PERIOD FOR REPLY IS SET TO EXPIRE 3 MONTH(S) OR THIRTY (30) DAYS, WHICHEVER IS LONGER, FROM THE MAILING DATE OF THIS COMMUNICATION.

- Extensions of time may be available under the provisions of 37 CFR 1.136(a). In no event, however, may a reply be timely filed after SIX (6) MONTHS from the mailing date of this communication.
- If NO period for reply is specified above, the maximum statutory period will apply and will expire SIX (6) MONTHS from the mailing date of this communication.
- Failure to reply within the set or extended period for reply will, by statute, cause the application to become ABANDONED (35 U.S.C. § 133). Any reply received by the Office later than three months after the mailing date of this communication, even if timely filed, may reduce any earned patent term adjustment. See 37 CFR 1.704(b).

Status

1)☒ Responsive to communication(s) filed on *5/29/08*.

2a)☐ This action is **FINAL**. 2b)☒ This action is non-final.

3)☐ Since this application is in condition for allowance except for formal matters, prosecution as to the merits is closed in accordance with the practice under *Ex parte Quayle*, 1935 C.D. 11, 453 O.G. 213.

Disposition of Claims

4)☒ Claim(s) *1,3,4,6-9,11-13,17,19,20,22-25 and 38* is/are pending in the application.

4a) Of the above claim(s) *7-9* is/are withdrawn from consideration.

5)☐ Claim(s) _____ is/are allowed.

6)☒ Claim(s) *1,3,4,6,11-13,17,19,20,22-25 and 38* is/are rejected.

7)☐ Claim(s) _____ is/are objected to.

8)☐ Claim(s) _____ are subject to restriction and/or election requirement.

Application Papers

9)☐ The specification is objected to by the Examiner.

10)☐ The drawing(s) filed on _____ is/are: a)☐ accepted or b)☐ objected to by the Examiner.

Applicant may not request that any objection to the drawing(s) be held in abeyance. See 37 CFR 1.85(a).

Replacement drawing sheet(s) including the correction is required if the drawing(s) is objected to. See 37 CFR 1.121(d).

11)☐ The oath or declaration is objected to by the Examiner. Note the attached Office Action or form PTO-152.

Priority under 35 U.S.C. § 119

12)☐ Acknowledgment is made of a claim for foreign priority under 35 U.S.C. § 119(a)-(d) or (f).

a)☐ All b)☐ Some * c)☐ None of:

1.☐ Certified copies of the priority documents have been received.

2.☐ Certified copies of the priority documents have been received in Application No. _____.

3.☐ Copies of the certified copies of the priority documents have been received in this National Stage application from the International Bureau (PCT Rule 17.2(a)).

* See the attached detailed Office action for a list of the certified copies not received.

Attachment(s)

1) ☒ Notice of References Cited (PTO-892)
2) ☐ Notice of Draftsperson's Patent Drawing Review (PTO-948)
3) ☐ Information Disclosure Statement(s) (PTO/SB/08) Paper No(s)/Mail Date _____.
4) ☐ Interview Summary (PTO-413) Paper No(s)/Mail Date. _____.
5) ☐ Notice of Informal Patent Application
6) ☐ Other: _____.

DETAILED ACTION

1. Applicant's amendment, filed 05/29/2008, has been entered.

Claims 1, 3, 4, 11, 12, 17, 19, 20, 22-25 and 38 have been amended.

Claims 1, 3, 4, 6-9, 11-13, 17, 19, 20, 22-25 and 38 are pending.

Again for the record and as pointed out previously, applicant's election of species (B), drawn to methods using an anti-PSGL-1 antibody and an agent that binds to the antibody and induces the cross-linking of a plurality of PSGL-1 antigens on the cell surface without traverse in the Reply, filed 07/22/2004, and the species autoimmune disease and type I diabetes in the Reply, filed 03/10/2004, has been acknowledged.

Claims 1, 3, 4, 6, 11-13, 17, 19, 20, 22-25 and 38 are under consideration in the instant application.

Claims 7-9 have been withdrawn from consideration by the examiner 37 CFR 1.142(b), as being drawn to a nonelected invention or species.

Claims 2, 5, 10, 14-16, 18, 21, and 26-37 have been canceled previously.

2. The text of those sections of Title 35 USC not included in this Action can be found in a prior Office Action.

3. Applicant's submission of an Information Disclosure Statement, filed 08/27/2008, is acknowledged.

The references cited in the Information Disclosure Statement, filed 08/27/2008 have been considered, but will not be listed on any patent resulting from this application because they were not provided on a separate list in compliance with 37 CFR 1.98(a)(1). In order to have the references printed on such resulting patent, a separate listing must be filed within the set period for reply to this Office action.

4. Priority.

Applicant submits that the applicant has previously addressed this issue and respectfully disagrees, but acknowledges the examiner's argument of record.

The following is reiterated for applicant's convenience.

As indicated previously, the filing date of the instant claims is deemed to be the filing date of the instant application USSN 10/051,497, filed 01/18/2002;

as the previous provisional priority application USSN 60/310,196, filed 08/03/2001, does not appear to provide sufficient written description for the claimed "limitations".

Applicant's assertions, filed 02/01/2007, concerning the priority of the instant invention back to priority USSN 60/310,196, filed 8/3/01, are acknowledged.

Applicant's arguments and the examiner's rebuttal are essentially the same of record.

As indicated in the previous Office Action, mailed 07/31/2006,
these assertions have not been found convincing essentially for the reasons of record reiterated herein for applicant's convenience.

As indicated previously, the instant claims now recite limitations which were not clearly disclosed in the priority provisional application as well as the specification as-filed, and would have changed the scope of the priority application and do change the scope of the instant disclosure as-filed.

For example, it cannot be said that a subgenus is necessarily described by a genus encompassing it and a species upon which it reads. See In re Smith 173 USPQ 679, 683 (CCPA 1972) and MPEP 2163.05.

Therefore, applicant's reliance on generic methods to reduce T cell-mediated immune responses with PSGL-1-specific antibodies and certain limitations found in the Examples of the provisional application does not provide sufficient written description for the claimed limitations indicated previously and herein, as currently claimed.

As indicated previously, the filing date of the instant claims as they read on "methods of preventing or reducing a T cell-mediated immune responses in an individual, including the "selecting an individual diagnosed", "administering a compound … induces a signal transduction pathway that results in the death of the T cell" (e.g. claim 1), "an agent that binds to the monoclonal antibody and induces the cross-linking of a plurality of PSGL-1 antigens on the surface of the T cell" (e.g. claim 4), detecting the number of T cells in a first biological sample (e.g. claims 13-14), "20% of peripheral blood $CD3^+$ cells (e.g. claims 15-16) and "diabetes" (e.g. elected autoimmune disease) is deemed to be the filing date of the instant application USSN 10/051,497, filed 8/3/01, as the previous provisional priority application does not appear to provide sufficient written description for the claimed "limitations" indicated herein.

Here, with respect to the recitation of "detecting the number of T cells in a first biological sample",
applicant relies upon Example 6 of the provisional application USSN 60/310,196, filed 08/03/2001 and likewise Example 6 of the instant application, USSN 10/051,497 to support the description above, via the administration of an anti-PSGL antibody TAB4 to experimental mice, measuring the percentage of $CD3^+$ T cells in harvested spleen and peripheral blood and comparing these results with corresponding results from untreated mice.
Applicant continues to assert that this comparison of control and treated mice is tantamount to what is claimed in claim 13.
However, as pointed out previously, applicant is relying upon a limited experimental study measuring certain parameters under certain defined conditions, while the claims are broader in scope or breadth.

It is acknowledged that page 15, lines 14-20 of the provisional application USSN 60/310,196, filed 08/03/2001, provides written description for targeting "diabetes mellitus" with anti-TAIP compounds (i.e., anti-PSGL-1 compounds)

Although applicant disagrees with this analysis, applicant has not presented a convincing detailed analysis as to why the claimed subject matter has clear support in the parent application, other than to assert that the provisional application provides ample written description for each and every limitation as presented and citing certain passages of the provisional application without sufficiently pointing out written support for the "limitations" indicated previously and herein.

Again, applicant is invited to verify the priority date of the instant claims, including written support and enablement under 35 USC 112, first paragraph.

Again, if applicant disagrees, applicant should present a detailed analysis as to why the claimed subject matter has clear support in the parent application. Applicant is invited to verify the priority date of the instant claims, including written support and enablement under 35 USC 112, first paragraph.

5. Upon reconsideration, including applicant's arguments, filed 05/29/2008, the previous rejections under 35 U.S.C. § 112, first paragraph, written description / new matter and enablement have been withdrawn.

6. New Grounds of Rejection.

As indicated previously, the prior art rejection were withdrawn in view of applicant's amended claims filed 10/26/2007, based upon the inclusion of the "selecting step".

However, upon reconsideration of the broadest reasonable interpretation of the claims, including the "selecting step", the prior art rejections of record with some modifications have been re-instated.

Under the broadest reasonable interpretation of the claims, including the recitation of the "selecting step" and the "wherein clause", the following is noted.

The broadest reasonable interpretation of the recitation of
"comprising: selecting an anti-PSGL-1 antibody that specifically binds to P-Selectin Glycoprotein Ligand-1 (PSGL-1) on the surface of an activated T cell, wherein the selecting is based on ability of the anti-PSGL-1 antibody to induce apoptosis of the activated T cell;".
is as follows.

"Selecting an anti-PSGL-1 antibody that specifically binds to P-Selectin Glycoprotein Ligand-1 (PSGL-1) on the surface of an activated T cell" simply reads on "making a choice or a selection", wherein the ordinary artisan is simply selecting/choosing an anti-PSGL-1 antibody from among several anti-PSGL-1 antibodies.

Therefore, the selection of any anti-PSGL-1 antibody with the property or characteristic of "inducing apoptosis of the activated T cell" meets the claimed method.

Also, the recitation of "wherein the selecting is based on ability of the anti-PSGL-1 antibody to induce apoptosis of the activated T cell;" can simply be read as a product-by-process limitation.

With respect to product-by-process limitations, the patentability of a product does not depend on its method of production. In re Thorpe, 227 USPQ 964, 966 (Fed. Cir. 1985).

Once the examiner provides a rationale tending to show that the claimed product appears to be the same or similar to that of the prior art, although produced by a different process, the burden shifts to applicant to come forward with evidence establishing an unobvious difference between the claimed product and the prior art product. In re Marosi, 218 USPQ 289, 292 (Fed. Cir. 1983).

See MPEP 2113.

In addition, regarding the interpretive "wherein clause" recited in claim 1,
the "wherein clause" does not recite any additional active method steps, but simply states a characterization or conclusion of the results of those steps.
Therefore, the "wherein clause" is not considered to further limit the method defined by the claim and has not been given weight in construing the claims.
See Texas Instruments, Inc. v. International Trade Comm., 26 USPQ2d 1018, 1023 (Fed Cir. 1993) ("A 'whereby' clause that merely states the result of the limitations in the claim adds nothing to the patentability or substance of the claim.").
Also, see Minton v. National Assoc. of Securities Dealers, Inc., 67 USPQ2d 1614, 1620 (Fed. Cir. 2003) ("A whereby clause in a method claim is not given weight when it simply expresses the intended result of a process step positively recited.").
See MPEP 2111.04.

Furthermore, additional evidence has been provided herein to support the applicability of the prior art anti-PSGL-1 antibodies, including Y1 and KPL-1, as well as their multivalent forms, to the claimed methods encompassing the "ability of the anti-PSGL-1 antibody to induce apoptosis of the activated T cell".

With respect to the ability of the "ability of the prior art anti-PSGL-1 antibody to induce apoptosis of the activated T cell", the following is noted.

As evidenced by the instant specification, Example 10 on pages 26-27 of the instant specification provides evidence that the KPL-1 antibody and KPL-1 antibody specificity is consistent with the claimed methods of employing anti-PSGL-1 antibodies that induce apoptosis of activated T cells.

Example 10: Induction of Apoptosis in Human T Cells by an ant-PSGL-1 Antibody

To determine the role played by PSGL-1 in the apoptosis of human T cells, time-course experiments were carried out to investigate when activated human T cells acquire sensitivity toward PSGL-l-mediated apoptotic signals. Human T cells were stimulated ~.5 with phytohemagglutinin (PHA) mitogen and further expanded in IL-2-containing medium. Activated T cells were harvested and then challenged with anti-PSGL-1 in the presence of IL-2 and cross-linking antibodies.

Human peripheral blood was taken from healthy adults, heparinized, and enriched for peripheral blood mononuclear cells (PBMC) based on differential density using Ficoll-Paque Plus (Pharmacia Biotech). The PBMC were activated with 1% PHA (Life Technologies, GibcoBRL) for 48 hours and subsequently maintained in recombinant human IL-2 (5 ng/ml) through the assay period. To assess the apoptosis-inducing ability of an anti-human PSGL-1 antibody, the activated cells were treated with: (1) 1 ug/ml of the anti-PSGL-1 antibody clone KPL-1 (BD PharMingen) plus cross-linker rabbit anti-mouse Ig (0.5 ug/ml) (Jackson ImmunoResearch Laboratories); (2) isotype control purified mouse Ig plus cross-linker rabbit anti-mouse Ig; or (3) cross-linker rabbit anti-mouse Ig alone. After six hours of treatment, the percentage of early apoptotic cells was determined by FACS, staining with anti-Annexin V (BD PharMingen) and PI (Sigma).

As shown in Fig. 8, signaling triggered by PSGL-1 using an anti-PSGL-1 antibody plus the crosslinker triggered significant level of apoptosis in PHA-activated human PBMC (mainly T cells). The percentage of apoptotic cells increased from 8.5% on days 3 to 24% on day 8 in anti-PSGL1 treated cultures. Neither isotopic-matched control, nor the cross-linking antibodies alone, had any effect on these cells.

Also, as evidenced by the Lin 132 Declaration, filed 02/01/2007.
the Lin 132 Declaration, filed 02/01/2007, acknowledges that KPL1-specific PSGL-1-specific antibodies can induce apoptosis (e.g., see Exhibit C; including Figure B(2b) on page 10; Figure C(1a) on page 12; Figure C(2a) on page 13).

Therefore, applicant's own disclosure (Example 10 of the instant specification) and own 132 Declaration (Lin Declaration) support the ability of the prior art anti-PSGL-1 antibody to induce apoptosis.

7. As pointed out previously, the prior art rejections have been extended to read on the species of administering anti-PSGL-1 antibodies in the absence of administering a secondary "cross-linking agent".

It does not appear that the claim language or limitations result in a manipulative difference in the method steps when compared to the prior art disclosures of administering anti-PSGL-1 antibodies that can induce apoptosis, including reducing an excessive or unwanted T cell mediated immune response, such as the elected autoimmune disease diabetes.

However, certain prior art disclosures are silent on the claimed recitation of "apoptosis-inducing anti-PSGL-1 antibody or antigen-binding fragment thereof" "wherein the binding of the antibody or antigen-binding fragment thereof to PSGL-1 on the surface of the T cell or NK cell induces apoptosis of the T cell or NK cell".

Also, as noted herein and of record, co-inventors own publication Chen et al. (Blood 104: 3233-3242, 2004) indicates that PSGL-1 mediated death via PSGL-1-specific antibodies is stage dependent in that it affects mature activated T cells (see entire document, particularly the Discussion).

Therefore, applicant's reliance on "the ability of anti-PSGL-1 antibodies to induce apoptosis" in the individual" appears based not entirely on the nature of the anti-PSGL-1 antibody but rather based on the presence of PSGL-1 expressing mature activated T cells.

In further evidence of the prior art teachings,
Levanon et al. (US 2005/0152906) teach that cross-linking of anti-PSGL-1 antibody leads to a apoptotic mechanism that contributes to cell killing (e.g., see paragraph [0190], which can be mediated by Fc receptor bearing cells (e.g., see paragraph [0208]) .
In addition, Levanon et al. teach anti-PSGL-1 antibodies that lead to apoptotic mechanisms (e.g., see paragraphs [0041], [0124], [0126], [0127], [0190] – [0195], [0206] – [0212]
and that such anti-PSGL-1 antibodies bind tyrosine-sulfated peptides (e.g., see paragraphs [0001], [0023], [0028], [0029], [0117] – [0136], [0177] - [0186], [0242] – [0251] and [0271]).
Therefore, the prior art teachings by Larsen et al. of employing antibodies that bind sulfated tyrosines would have the inherent property of inducing apoptosis.

8. New Ground of Rejection.

Claims 1, 3, 6, 11-12, 17, 19, 22-24 and 38 are rejected under 35 U.S.C. § 102(b) as being anticipated by Larsen et al. (U.S. Patent No. 5,840,679) (of record) (see entire document) essentially for the reasons of record and in further evidence of Chen et al. (Blood 104: 3233-3242, 2004) (of record) and Levanon et al. (US 2005/0152906).

Larsen et al. teaches methods of treating conditions characterized by P-selectin mediated intercellular adhesion, including inflammatory conditions, autoimmune conditions such as diabetes (see columns 15-16, overlapping paragraph) with neutralizing anti-PSGL-1 antibodies, including monoclonal antibodies (e.g. see column 18, paragraphs 2-4).

Although the reference is silent about the induction of apoptosis well as identifying the T cell as activated, $CD3^+$, $CD4^+$, or $CD8^+$ as well as the depletion of T cells, it does not appear that the claim language or limitations result in a manipulative difference in the method steps when compared to the prior art disclosure. See Bristol-Myers Squibb Company v. Ben Venue Laboratories 58 USPQ2d 1508 (CAFC 2001). "{i}t is a general rule that merely discovering and claiming a new benefit of an old process cannot render the process again patentable." In re Woodruff, 16 USPQ2d 1934, 1936 (Fed. Cir. 1990). The mechanism of action does not have a bearing on the patentability of the invention if the invention was already known or obvious. Mere recognition of latent properties in the prior art does not render nonobvious an otherwise known invention. In re Wiseman, 201 USPQ 658 (CCPA 1979). Granting a patent on the discovery of an unknown but inherent function would remove from the public that which is in the public domain by virtue of its inclusion in, or obviousness from, the prior art. In re Baxter Travenol Labs, 21 USPQ2d 1281 (Fed. Cir. 1991). See MPEP 2145.

Although the reference is silent about selecting an individual diagnosed as having or as being at risk of acquiring a condition characterized by an excessive or unwanted T cell-mediated immune response, such limitations are anticipated by the targeted conditions and diseases described in columns 15-16, overlapping paragraph, because the ordinary artisan would have had to diagnose a patient with such a condition or disease in order to treat said condition or disease.

Also, a species will anticipate a claim to a genus. See MPEP 2131.02.

The claimed functional limitations, including the induction of apoptosis and the targeted cell populations and the mechanism of action, would be inherent properties of the referenced methods to treat a number of conditions and diseases with anti-PSGL-1 antibodies, which block the P-selectin ligand adherence function, abolish or markedly reduce inflammation (e.g. see columns 18-19, overlapping paragraph) and anti-PSGL-1 antibodies that bind the sulfated tyrosine residues of PSGL-1 (e.g., see columns 7-8, overlapping paragraph; column 9, paragraph 1; column 12, paragraph 2; column 18, paragraph 2; Example 10 on columns 33-36 and Example 13, on column 42).

Here, too, it is noted that target cells targeted by anti-PSGL-1 antibody may eliminated by ADCC (see column 19, lines 5-13).

In further evidence of the prior art teaching,
co-inventors own publication Chen et al. (Blood 104: 3233-3242, 2004) indicates that PSGL-1 mediated death via PSGL-1-specific antibodies is stage dependent in that it affects mature activated T cells (see entire document, particularly the Discussion).
Therefore, Chen et al. teach the cell stage dependence of the ability of anti-PSGL-1 antibodies to induce apoptosis in the claimed methods.

In further evidence of the prior art teachings,
Levanon et al. (US 2005/0152906) teach that cross-linking of anti-PSGL-1 antibody leads to a apoptotic mechanism that contributes to cell killing (e.g., see paragraph [0190], which can be mediated by Fc receptor bearing cells (e.g., see paragraph [0208]) .
In addition, Levanon et al. teach anti-PSGL-1 antibodies that lead to apoptotic mechanisms (e.g., see paragraphs [0041], [0124], [0126], [0127], [0190] – [0195], [0206] – [0212]
and that such anti-PSGL-1 antibodies bind tyrosine-sulfated peptides (e.g., see paragraphs [0001], [0023], [0028], [0029], [0117] – [0136], [0177] - [0186], [0242] – [0251] and [0271]).
Therefore, the prior art teachings by Larsen et al. of employing antibodies that bind sulfated tyrosines would have the inherent property of inducing apoptosis.

With respect to applicant's arguments and the examiner's rebuttal concerning this rejection, the following is reiterated for applicant's convenience.

Applicant's arguments in conjunction with the Lin 132 Declaration of record have been fully considered but are not found convincing essentially for the reasons of record.

Applicant has submitted in conjunction with the Lin Declaration that not all anti-PSGL-1 antibodies can induce T cell apoptosis.
Applicant has relied upon the assertion that applicant has discovered a new epitope specificity if apoptosis-inducing anti-PSGL-1 antibodies.

However, it has been noted that the claims do not recite a particular antibody epitope per se.

Applicant in conjunction with the Lin 132 Declaration disagrees with that the position of the examiner that the evidentiary reference Chen indicates that it is the presence of PSGL-1 on mature activated T cells (e.g., cell stage dependent) that governs the claimed mode of action rather than the nature (e.g. apoptosis-inducing anti-PSGL-1 antibody).

Applicant's reliance upon the recitation of "apoptosis inducing anti-PSGL-1 antibody and "the binding of the antibody or antigen-binding fragment thereof to PSGL-1 on the surface of the T cell or NK cell induces apoptosis of the T cell or NK cell to obviate this rejection has been acknowledged.

Applicant's arguments in conjunction with the Lin 132 Declaration noting that certain anti-PSGL-1 antibodies, but not all anti-PSGL-1 antibodies, are capable inducing apoptosis or mature, activated T cells and that certain apoptosis-inducing anti-PSGL-1 antibodies do not interfere with PSGL-1-mediated interactions with other selectins has been acknowledged.

More pointedly, applicant has asserted in conjunction with the Lin 132 Declaration that neutralizing and non-neutralizing antibodies taught by the prior art Larsen et al. would <u>not</u> necessarily and inevitably involve anti-PSGL-1 antibodies that are capable of inducing apoptosis of T cells.

Applicant further submits that Larsen et al. is silent about apoptosis as well as the cross-linking of anti-PSGL-1 antibodies by any means.

However, applicant in conjunction with the Lin Declaration have indicated that the claimed methods and modes of action rely upon secondary cross-linking agents/antibodies and/or in the absence of secondary cross-linking agents/antibodies (e.g., via Fc receptors).

As noted by co-inventors own publication Chen et al. (Blood 104: 3233-3242, 2004), the issue appears not to be one of agonistic or antagonistic antibodies but rather the presence of PSGL-1 expressing mature activated T cells during the administration of PSGL-1-specific antibodies.

Rather, much of applicant's arguments in conjunction with the Lin Declaration appeared to rely upon an asserted new mechanism of action of anti-PSGL-1 antibodies rather than focusing on new anti-PSGL-1 antibody epitopes or other characteristics.
Also, the anti-PSGL-1 antibodies are claimed in terms of function (e.g., apoptosis-inducing).

Again, the mechanism of action does not have a bearing on the patentability of the invention if the invention was already known or obvious. Even though applicant has proposed or claimed the mechanism by which anti-PSGL-1 antibodies may reduce T cell mediated immune responses does not appear to distinguish the prior art teaching the same or nearly the same methods to achieve the same end result.

Further, it has been noted in the in teachings of Larsen et al. concerning PSGL-1-specific inhibitory antibodies, such PSGL-1-specific neutralizing antibodies bind to PSGL-1, or to complex carbohydrate moieties characteristic of PSGL-1 (e.g., see column 18, paragraph 2) as well as inhibitory antibodies that bind particularly fragments of PSGL-1, including peptides having a sulfated tyrosine (e.g., see column 18, paragraph 4) and exemplified anti-PSGL-1 antibodies that demonstrated complete inhibition of PSGL-1 : P-selectin binding (e.g., see Example 7 on columns 29-30) as well as providing appropriate screening assays (e.g., see columns 19-20; Example 7 on columns 29-30).

Given these specificities and properties of neutralizing anti-PSGL-1 antibodies to be employed in therapeutic methods to treat diabetes
and the lack of a requirement for additional cross-linking antibodies / agents to be administered in combination;
it does not appear that the claim language or limitations result in a manipulative difference in the method steps when compared to the prior art disclosure.
See Bristol-Myers Squibb Company v. Ben Venue Laboratories 58 USPQ2d 1508 (CAFC 2001).
See M.P.E.P. 2145.

The products employed in the instant methods and the prior art are defined in terms of anti-PSGL-1 antibodies. Comparison of the instant products with prior art is difficult since the Office is not equipped to manufacture the claimed product and/or prior art products that appear to be related and conduct comparisons

9. New Grounds of Rejection.

Although Lazarovits et al. (US 2004/0002450 A1) does not teach treating the elected species of diabetes per se, Lazarovits et al. does teach treating autoimmune diseases with PSGL-1-specific antibodies that appear to be consistent with applicant's arguments and interpretation of "apoptosis-inducing PSGL-1 antibodies".

Claims 1, 3, 4, 6, 11-13, 17, 19, 20, 22-25 and 38 are rejected under 35 U.S.C. § 102(e) as being anticipated by Lazarovits et al. (US 2004/0002450 A1) (of record) (see entire document) and as further evidenced by the Lin 132 Declaration, filed 02/01/2007, Example 10 of the instant specification,
and in further evidence of Chen et al. (Blood 104: 3233-3242, 2004) and Levanon et al. (US 2005/0152906).

Lazarovits et al. teach methods of treating inflammation, including autoimmune diseases with PSGL-1-specific antibodies (e.g., see paragraphs [00555] – [0057]; Summary of the Invention on paragraphs [0059] – [0144]; Detailed Description of the Invention) , including the Y1, Y17 and KPL1 epitopic specificities (e.g., see Selectins and PSGL-1 on paragraphs [0029] – [0042] ; Summary of the Invention; Detailed Description of the Invention; and Examples), including antibody constructs (e.g., see paragraphs [0474] – [0523]) as well as their use to monitor disease states (e.g., see paragraph 0523]).

The Lin 132 Declaration, filed 02/01/2007, acknowledges that KPL1-specific PSGL-1-specific antibodies can induce apoptosis (e.g., see Exhibit C).

As evidenced by the instant specification, Example 10 on pages 26-27 of the instant specification provides evidence that the KPL-1 antibody and KPL-1 antibody specificity is consistent with the claimed methods of employing anti-PSGL-1 antibodies that induce apoptosis of activated T cells.

Also, as evidenced by the Lin 132 Declaration, filed 02/01/2007.
the Lin 132 Declaration, filed 02/01/2007, acknowledges that KPL1-specific PSGL-1-specific antibodies can induce apoptosis (e.g., see Exhibit C; including Figure B(2b) on page 10; Figure C(1a) on page 12; Figure C(2a) on page 13).

Therefore, applicant's own disclosure (Example 10 of the instant specification) and own 132 Declaration (Lin Declaration) support the ability of the prior art anti-PSGL-1 antibody to induce apoptosis.

In further evidence of the prior art teaching,
co-inventors own publication Chen et al. (Blood 104: 3233-3242, 2004) indicates that PSGL-1 mediated death via PSGL-1-specific antibodies is stage dependent in that it affects mature activated T cells (see entire document, particularly the Discussion).

Therefore, Chen et al. teach the cell stage dependence of the ability of anti-PSGL-1 antibodies to induce apoptosis in the claimed methods.

In further evidence of the prior art teachings,
Levanon et al. (US 2005/0152906) teach that cross-linking of anti-PSGL-1 antibody leads to a apoptotic mechanism that contributes to cell killing (e.g., see paragraph [0190], which can be mediated by Fc receptor bearing cells (e.g., see paragraph [0208]) .
In addition, Levanon et al. teach anti-PSGL-1 antibodies that lead to apoptotic mechanisms (e.g., see paragraphs [0041], [0124], [0126], [0127], [0190] – [0195], [0206] – [0212] and that such anti-PSGL-1 antibodies bind tyrosine-sulfated peptides (e.g., see paragraphs [0001], [0023], [0028], [0029], [0117] – [0136], [0177] - [0186], [0242] – [0251] and [0271]).
Therefore, the prior art teachings by Larsen et al. of employing antibodies that bind sulfated tyrosines would have the inherent property of inducing apoptosis.

The claimed functional limitations would be inherent properties of the referenced PSGL-1-specific antibodies in methods to treat certain inflammatory diseases, including autoimmune diseases.

It does not appear that the claim language or limitations result in a manipulative difference in the method steps when compared to the prior art disclosure.
See Bristol-Myers Squibb Company v. Ben Venue Laboratories 58 USPQ2d 1508 (CAFC 2001).
"{i}t is a general rule that merely discovering and claiming a new benefit of an old process cannot render the process again patentable". In re Woodruff, 16 USPQ2d 1934, 1936 (Fed. Cir. 1990). The mechanism of action does not have a bearing on the patentability of the invention if the invention was already known or obvious. Mere recognition of latent properties in the prior art does not render nonobvious an otherwise known invention. In re Wiseman, 201 USPQ 658 (CCPA 1979). Granting a patent on the discovery of an unknown but inherent function would remove from the public that which is in the public domain by virtue of its inclusion in, or obviousness from, the prior art. In re Baxter Travenol Labs, 21 USPQ2d 1281 (Fed. Cir. 1991). See M.P.E.P. 2145.

10. New Grounds of Rejection.

Claims 1, 3, 4, 6, 11-13, 17, 19, 20, 22-25 and 38 are rejected under 35 U.S.C. § 103(a) as being unpatentable over by Larsen et al. (U.S. Patent No. 5,840,679)

in view of Lazarovits et al. (US 2004/0002450 A1) (of record)

in view of Trembleau et al. (J. Immunol. 163 : 2960 – 2968, 1999) (of record), Yago et al. (J. Immunol. 161 : 1140 –1145 (1998) (of record), Hirata et al. (J. Exp. Med. 192: 1669 – 1675, 2000) (of record) and Cobbold et al. (U.S. Patent No. 6,056,956) (of record)

and as further evidenced by the Lin 132 Declaration, filed 02/01/2007, Example 10 of the instant specification,

and as evidenced by Chen et al. (Blood 104: 3233-3242, 2004) (of record) and Levanon et al. (US 2005/0152906).

Larsen et al. teaches methods of treating conditions characterized by P-selectin mediated intercellular adhesion, including inflammatory conditions, autoimmune conditions such as diabetes (see entire document, including columns 15-16, overlapping paragraph) with neutralizing anti-PSGL-1 antibodies, including monoclonal antibodies (e.g. see column 18, paragraphs 2-4).

Further, the reason or motivation to modify the reference may often suggest what the inventor has done, but for a different purpose or to solve a different problem. It is not necessary that the prior art suggest the combination to achieve the same advantage or result discovered by applicant. See MPEP 2144.

Also, it is not a requirement that an inventor set forth or even know how or why the invention works. Newman v. Quigg, 11 USPQ2d 1340 (Fed. Cir. 1989).

Therefore, the prior art clearly provides for the administration of anti-PSGL-1 antibody to inhibit adhesion via PSGL-1/P-selectin interactions, inflammation and autoimmunity, including diabetes (elected species). While the prior art does not explicitly teach the induction of T cell or NK cell death, the prior art clearly provides for the same or nearly the same desired endpoints by administering the same antagonists to the same patient populations encompassed by the claimed methods. Again, it does not appear that the claim language or limitations result in a manipulative difference in the method steps when compared to the prior art disclosure

Although the reference is silent about selecting an individual diagnosed as having or as being at risk of acquiring a condition characterized by an excessive or unwanted T cell-mediated immune response, such limitations are expected by the targeted conditions and diseases described in columns 15-16, overlapping paragraph of Larsen et al., because the ordinary artisan would have had to diagnose a patient with such a condition or disease in order to treat said condition or disease.

Larsen et al. differs from the claimed methods by not disclosing the art known monitoring of T cells and NK cells in therapeutic methods.

Lazarovits et al. teach methods of treating inflammation, including autoimmune diseases with PSGL-1-specific antibodies (e.g., see paragraphs [00555] – [0057]; Summary of the Invention on paragraphs [0059] – [0144]; Detailed Description of the Invention) , including the Y1, Y17 and KPL1 epitopic specificities (e.g., see Selectins and PSGL-1 on paragraphs [0029] – [0042] ; Summary of the Invention; Detailed Description of the Invention; and Examples), including antibody constructs (e.g., see paragraphs [0474] – [0523]) as well as their use to monitor disease states (e.g., see paragraph 0523]).

Snapp et al. teach the KPL1 anti-PSGL-1 antibody specificity, wherein KPL1 completely inhbiting P-selectin-mediated interactions, including interactions with lymphoid cells such as T cells and NK cells (see entire document, including Abstract, Results and Discussion).

With respect to the evidentiary references supporting that the prior art meets the claimed recitation of the ability of anti-PSGL-1 antibodies to induce apoptosis,
the following is noted.

As evidenced by the instant specification, Example 10 on pages 26-27 of the instant specification provides evidence that the KPL-1 antibody and KPL-1 antibody specificity is consistent with the claimed methods of employing anti-PSGL-1 antibodies that induce apoptosis of activated T cells.

Also, as evidenced by the Lin 132 Declaration, filed 02/01/2007.
the Lin 132 Declaration, filed 02/01/2007, acknowledges that KPL1-specific PSGL-1-specific antibodies can induce apoptosis (e.g., see Exhibit C; including Figure B(2b) on page 10; Figure C(1a) on page 12; Figure C(2a) on page 13).

Therefore, applicant's own disclosure (Example 10 of the instant specification) and own 132 Declaration (Lin Declaration) support the ability of the prior art anti-PSGL-1 antibody to induce apoptosis.

In further evidence of the prior art teachings,
Levanon et al. (US 2005/0152906) teach that cross-linking of anti-PSGL-1 antibody leads to a apoptotic mechanism that contributes to cell killing (e.g., see paragraph [0190], which can be mediated by Fc receptor bearing cells (e.g., see paragraph [0208]) .
In addition, Levanon et al. teach anti-PSGL-1 antibodies that lead to apoptotic mechanisms (e.g., see paragraphs [0041], [0124], [0126], [0127], [0190] – [0195], [0206] – [0212]
and that such anti-PSGL-1 antibodies bind tyrosine-sulfated peptides (e.g., see paragraphs [0001], [0023], [0028], [0029], [0117] – [0136], [0177] - [0186], [0242] – [0251] and [0271]).
Therefore, the prior art teachings by Larsen et al. of employing antibodies that bind sulfated tyrosines would have the inherent property of inducing apoptosis.

The claimed functional limitations would be intrinsic or expected properties of the referenced PSGL-1-specific antibodies in methods to treat certain inflammatory diseases, including autoimmune diseases.

Also, in further evidence of the prior art teaching,
co-inventors own publication Chen et al. (Blood 104: 3233-3242, 2004) indicates that PSGL-1 mediated death via PSGL-1-specific antibodies is stage dependent in that it affects mature activated T cells (see entire document, particularly the Discussion).
Therefore, Chen et al. teach the cell stage dependence of the ability of anti-PSGL-1 antibodies to induce apoptosis in the claimed methods.

In addition to the teachings above and with respect to the role PSGL-1 and T cells and NK cells, the following is noted.

Trembleau et al. teach T cell recruitment in the pancreas favored by IL-12-deficient NOD mice, as revealed by increased P-selectin ligand expression on pancreas-infiltrating T cells and, this could, at least in part, compensate for the defective Th1 cell pool recruitable from peripheral lymphoid organs (see entire document, including the Abstract and Discussion). Also, this reference discusses the role of T cells in autoimmunity, including diabetes (see Introduction and Discussion).

Hirata et al. teach PSGL-1 mediated T helper lymphocyte migration in inflammation (see entire document, including the Abstract, Results and Discussion). The Results, including the Figures provide for monitoring the expression and function of PSGL-1-expressing T cells (see pages 1670-1674).

Yago et al. teach the role of PSGL-1/Pselectin interactions in the adhesion of NK cells, including the ability of anti-PSGL-1 antibodies to abolish such interactions (See entire document, including the Abstract and Discussion). Yago et al. teach the art known role of NK cells in various immune responses (see Introduction and Discussion).

In addition to the teachings above concerning monitoring,
Cobbold et al. teach monitoring T cell subsets and activities (e.g. mixed lymphocyte cultures) from individuals whom have been treated with immunosuppressive antibodies (see entire document, including columns 12-21, Tolerance and Anergy in Mice Grafted with Multiple Minor Antigen Mismatched Bone Marrow, Monitoring T cell Subsets for Depletion and Mixed Lymphocyte Cultures, The Effects of Combined Rat IgG2b Antibodies on Circulating T Cells, Tolerant Mice Can Still Respond In Vitro as well as Tables 2, 3, 4, 7 and 9).

Note that Cobbold et al. teach that it may be necessary to reduce a population of T cells to less than about 70% - 10% of their normal values in order to achieve the desired immunosuppressive endpoint (see column 4, paragraph 2).

Hirata et al. teach that the administration of anti-PSGL-1 antibodies could reduce the number of T cells migrating into an inflamed skin by 66% (see page 1672, Migration of PSGL-1deficient Th1 Cells into the Inflamed Skin is Impaired).

Given the teachings of the prior art that PSGL-1 was expressed on T cells, including T cells involved in inflammation and autoimmunity such as diabetes, as taught by Trembleau et al. and Hirata et al. in conjunction with the teachings of treating inflammation with anti-PSGL-1 antibodies as taught by Larsen et al., the ordinary artisan would have been motivated to monitor the presence and function of T cells as a result of anti-PSGL-1 treatment. Hirata et al. and Cobbold et al. both teach monitoring T cell numbers and function in response to the administration of antagonistic antibodies in vivo, including the administration of anti-PSGL-1.

Therefore, it would have been obvious to one of ordinary skill in the art at the time the invention was made to detect the number, viability and biological activity of T cells prior to and after the administration of an antagonistic anti-PSGL-1 antibody in inflammatory or autoimmune conditions such as diabetes to monitor the efficacy of antibody treatment, including measuring the control values prior to treatment.

Therefore, one of ordinary skill in the art would have had an expectation of success that the administration of antagonistic antibodies, including antibodies that bind T cells or NK cells, including anti-PSGL-1 antibodies, could reduce T cell populations by at least 20% or that anti-PSGL-1 antibody can abolish NK binding to P-selectin. Given that PSGL-1 is expressed on activated, $CD4^+$, $CD8^+$ T cells as well as NK cells targeted by anti-PSGL-1 antibody, one of ordinary skill in the art would have had sufficient motivation and expectation of success in monitoring the number, activity and viability of various targeted cells by the administration of anti-PSGL-1 antibodies in order to assess the efficacy of the treatment and the immune responses and capabilities of the patient, as indicated by Trembleau et al., Hirata et al. and Cobbold et al..

One of ordinary skill in the art at the time the invention was made would have been motivated to substitute the anti-PSGL-1 antibodies with the Y1, Y17 and KPL1 epitopic specificities in inhibiting inflammatory or autoimmune conditions targeted by PSGL-1 antagonists, given their highly inhibitory effects on PSGL-1-mediated interactions, including their antagonistic effects on lymphoid cells such as T cells and NK cells, as taught by Snapp et al. and Lazarovits. A person of ordinary skill in the art at the time the invention was made would have been motivated by taking the advantages of the specificities and properties of the highly inhibitory properties of the Y1, Y17 and KPL1 PSGL-1 epitopic specificities to modify the prior art teachings to treat inflammatory or autoimmune conditions with an expectation of success, since such properties and advantages are consistent with human therapeutic regimens associated with treating said conditions at the time the invention was made.

From the teachings of the references, it was apparent that one of ordinary skill in the art would have had a reasonable expectation of success in producing the claimed invention. Therefore, the invention as a whole was prima facie obvious to one of ordinary skill in the art at the time the invention was made, as evidenced by the references, especially in the absence of evidence to the contrary.

11. Upon reconsideration of applicant's Remarks concerning the cancellation of copending claims in USSN 10/662,906,
the previous provisional rejection under the judicially created doctrine of obviousness-type double patenting as being unpatentable over claims of copending application USSN 10/662,906 has been withdrawn.

12. No claim allowed.

13. Any inquiry concerning this communication or earlier communications from the examiner should be directed to Phillip Gambel whose telephone number is (571) 272-0844. The examiner can normally be reached Monday through Thursday from 7:30 am to 6:00 pm. A message may be left on the examiner's voice mail service. If attempts to reach the examiner by telephone are unsuccessful, the examiner's supervisor, Eileen O'Hara can be reached on (571) 272-0878.

The fax number for the organization where this application or proceeding is assigned is 571-272-8300.

Information regarding the status of an application may be obtained from the Patent Application Information Retrieval (PAIR) system. Status information for published applications may be obtained from either Private PAIR or Public PAIR. Status information for unpublished applications is available through Private PAIR only. For more information about the PAIR system, see http://pair-direct.uspto.gov. Should you have questions on access to the Private PAIR system, contact the Electronic Business Center (EBC) at 866-217-9197 (toll-free).

/Phillip Gambel/

Phillip Gambel, Ph.D., J.D.
Primary Examiner
Technology Center 1600
Art Unit 1644
September 2, 2008